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10/566,886	02/01/2006	David M. Neville	14028.0295U2	9182

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,886	NEVILLE ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *27-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending in this office action.

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-26) in the reply filed on 2/11/08 is acknowledged. The traversal is on the ground(s) that serious burden has not been demonstrated. This is not found persuasive. As regards search burden, the inventions of Group I and II are unrelated as they comprise distinct steps and utilize different products which demonstrate that each method has a different mode of operation. Each invention performs their function using a structurally and functionally divergent material as the methodology and materials necessary to express an immunotoxin in *Pichia* are significantly distinct from the methodology and materials necessary to purify a non-glycosylated immunotoxin. While the cells of Group I are used to prepare a culture comprising immunotoxin, this culture is not necessary for the method of Group II. The method of Group II t hat is directed to purification of the immunotoxin on an anion exchange column is not required for the method of Group I. Therefore, the methods of Group I and Group II lack unity of invention and are patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 27-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/11/08.

Specification

The abstract of the disclosure is objected to because it exceeds 150 words. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 1, line 23. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, figure 1, boxed sequence, contains a sequence that is not identified by sequence identifier number. If the sequences can be found in the sequence listing it would be remedial to insert the appropriate SEQ ID NO:s. If not, a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, CRF and letter stating that the contents of the sequence listing and the CRF are the same and contain no new matter is required. **The nature of the non-compliance did not preclude the examination on the merits of the instant application, the results of which follow.**

Claim Objections

Claims are objected to because of the following informalities: Claim 1 is objected to for in line 2 "an immunotoxin". For clarity, reference to previously recited limitations is by use of the article --the-- or said--. In this case, it would be remedial to recite --the immunotoxin--. Secondly, recitation "performing methanol induction of" requires amendment to --performing methanol induction on--. Thirdly, the recitation that "the methanol induction is at a temperature of below" is inaccurate since as the methanol induction is a step that is performed and cannot itself be a temperature. The term "of" is not required in the sentence and therefore, it would be remedial to recite, --the methanol induction is performed at a temperature below-- .

Claims 2 and 3 recite "the methanol induction is a limited methanol (methanol and glycerol) feed". However, the induction is a step of a method and is not feed. It would be remedial to recite --the methanol induction comprises a limited methanol (methanol and glycerol) feed--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the limitation "the 4:1 methanol glycerol induction feed" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 10 is drawn to a *Pichia* pastoris comprising a mutation in the amino acid sequence encoding EF-2. Therefore, applicants claim a genus of *Pichia* cells comprising mutant EF-2 sequences. The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The specification discloses a single sequence of EF-2 and that is represented by SEQ ID NO: 13. This sequence is used to generate a single species of cells wherein EF-2 is

mutated so that the Gly amino acid at position 701 has been changed to an Arg. This mutation results in a prevention of ADP-ribosylation of EF-2 in other organisms. Hence, applicants demonstrate a single species of cells and that is a cell in which EF-2 (SEQ ID NO:13) has a Gly to Arg mutation at position 701. The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a sequence requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution • of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Given the large size and diversity of cells and EF2 mutants and the inability to determine which will also have the essential element, it is concluded that the invention

must be empirically determined. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-10, 12, 13, 15-20 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al (US 6,723,536; see entire document) in view of Neville et al (WO 01/87982; see entire document).

Applicants claim a method of expressing an immunotoxin in *Pichia pastoris* comprising growth in enzymatic digest of protein and yeast extract upon which methanol induction is performed at a temperature below 17.5°C.

Neville et al teach expression of proteins in *Pichia pastoris* wherein growth in is enzymatic digest of protein and yeast extract which methanol induction. Growth media comprises 4% glycerol, *about* 2% yeast extract, 2% enzymatic digest of protein, 1.34% yeast nitrogen base with ammonium sulfate and without amino acids, .43% PTM1 solution, wherein growth occurs at pH 3.5, and 0.01% antifoaming agent. Dissolved oxygen is about 40% (see figure 41). Methanol induction is performed at pH 7.0 wherein the agitation is 800 rpm (about 400 rpm) see page 159. Casamino acids and yeast extract serve as a source of amino acids and PMSF for at least 2 hours (it maintained expression

level for 11 hours; see page 160, ¶ 2). Neville teach us of a mutant *Pichia pastoris* cell that comprises a mutation in the EF2 gene and is used for expression of A-dmDT390-bisFV(UCHT1) (see figure 20 and page 138, ¶ 4, page 55, line 1-5).

Neville et al do not teach that the temperature is below 17.5°C.

Madsen et al teach methods of producing recombinant proteins wherein *Pichia* cells are grown in media comprising enzymatic digestion of protein and yeast extract (see col 7-8). Methanol induction was performed wherein the induction was performed at less than 20°C and in some embodiments at 10°C (see col 7, line 35-44), which range encompasses 15°C. Glycerol containing media is fed to the glycerol containing cells and dissolved oxygen is 30% (see col 8, batch glycerol phase).

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte* Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In the instant case, the combination of Neville et al and Madsen et al demonstrates an attempt to use known techniques to improve similar methods of protein expression using *Pichia* based upon skill that was available at the time of filing with well-established methods. In the instant case, there are multiple overlapping methods used to cultivate *Pichia* for protein expression. Madsen et al is directed to teaching methods of methanol induction in which the temperature is low. Neville et al teach methods of expressing *diphtheria toxin* using *Pichia* using methanol induction. It would have been obvious to one skilled in the art to make a substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, the claims would have been obvious because a

particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 2, 4, 11, 14, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al (US 6,723,536; see entire document) in view of Neville et al (WO 01/87982; see entire document) as applied to claims 1, 3, 5-10, 12, 13, 15-20 and 22-25 above, and further in view of Magota et al (6,171,828; see entire document) and McGrew et al (Gene, 1997, Vol 187(2), pages 193-200; see entire document) and Chang et al (US 6,992,172; see entire document).

The teachings of Neville et al in view of Madsen et al are as above, except neither teaches specifically that methanol induction occurs by 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1. Nor do any of the previously cited references teach use of soy digest of protein.

Magota teaches methanol induction in which methanol is fed into the culture at a rate of between 1.5 ml/L/hr and 4.7 ml/L/hr (see figure 4) which correlates for a 10L culture to 0.25 to 0.78 ml/min.

McGrew et al teach that a glycerol:methanol feed can be used to successfully induce heterologous protein expression in *Pichia* cells wherein the ratio of glycerol to methanol is 4:1 (see table).

Chang et al teach that enhanced expression is accomplished by use of soytone which is a digest of soy protein (see e.g. col 59, line 29-55).

It would have been obvious to one skilled in the art to make a substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant rejection, Magota et al, McGrew et al and Chang et al demonstrate that methods involving expression of proteins from *Pichia* are known and recognized to use methanol induction wherein either 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1. As well, Chang et al teach that soytone in the media resulted in a plant-derived (rather than animal-derived) media component that lead to increased expression of recombinant protein (see e.g. 59, line 29-55). Furthermore, the claims would have been obvious because the techniques of methanol induction by 1) limited methanol feed of 0.5-0.75 ml/min/10L or 2) a glycerol:methanol feed wherein the ratio of glycerol to methanol is 4:1 as well as use of soytone were recognized as part of the ordinary capabilities of one skilled in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633

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